REVIEW ARTICLE

Reactive arthritis

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Summary

Reactive arthritis is a rare complication of certain infections. The similar features and HLA associations with the seronegative arthropathies have raised the possibility that the latter may be forms of reactive arthritis. This review describes the clinical and epidemiological features, and the recent advances in our understanding of the underlying pathogenesis of reactive arthritis.

Introduction

The term reactive arthritis was introduced by Aho *et al.* (1973) to describe several forms of joint disease associated with infection but in which the causative micro-organism cannot be isolated from the joint. This broad group of disorders, which includes Reiter's syndrome, can be divided into three categories (Table 1). Dumonde and Stewart (1978) distinguish between postinfective and reactive arthritis, the main difference being the presence or absence of microbial antigen in the joint. In clinical practice, however, it is rarely possible to demonstrate non-viable microbial antigen in the joint. The post-viral arthritides are mostly infectious, with the exception of the arthritis associated with hepatitis B and adenovirus infection, and that following vaccination for rubella. Only these three forms will therefore be discussed here.

The concept of reactive arthritis is an exciting one, firstly, because of the association between HLA antigen B27 and the enterocolitic and sexually acquired forms of reactive arthritis. When compared with the numerous other HLA disease associations this one is especially revealing since the responsible micro-organism is known. This has offered unique possibilities for speculation and experimentation to elucidate the roles of immune-regulatory genes and cross-reactivity in disease susceptibility. Secondly, this group of conditions has close clinical and experimental overlaps with the seronegative spondyl-

TABLE 1. Classification of the reactive arthritides

Group A.	
Acute rheumatic fever	
Reactive arthritis following gastrointestinal infection (enterocolitic or postdysenteric arthritis) with	
	<i>Salmonella typhimurium</i>
	<i>S. enteritidis</i>
	<i>Shigella flexneri</i>
	<i>Yersinia enterocolitica</i>
	<i>Campylobacter jejuni</i>
Sexually acquired reactive arthritis (SARA) following infection of the genito-urinary tract with	
	<i>Chlamydia trachomatis</i>
	<i>Neisseria gonorrhoeae</i>
	Mycoplasma-T?
	L-forms?
	Herpes genitalis virus?
Idiopathic reactive arthritis	
Group B.	
Erythema nodosum	
Group C.	
Virus-associated reactive arthritis—Hepatitis B	
	Adenovirus
	Rubella vaccination

arthritides, raising the possibility that these are also 'post-infective' syndromes.

Group A

Acute rheumatic fever

This serves as a possible model or prototype but only the points that best illustrate the various features of reactive arthritis will be described here. Infection with group A β -haemolytic streptococci produces a tonsillitis and, after a latent period (1-6 weeks, average 3), a small proportion (0.5-3%) of individuals develop acute rheumatic fever with polyarthritis (75%), carditis (50%) and chorea. This complication is more common in patients who are

blood group A, B and AB and salivary H substance secretors (Glynn and Holborow, 1961). Monozygotic twins have a higher concordance rate for rheumatic fever than do dizygotic twins, and their clinical manifestations are also more concordant (Spagnuolo and Taranta, 1968). No consistent HLA association has been shown (Caughey *et al.*, 1975; Aho *et al.*, 1979). Streptococci are rarely, if ever, isolated from the joints, heart or brain. Penicillin, when given at this stage, has no effect on the course of the disease. In a certain percentage of cases the acute inflammatory changes are followed by chronic post-inflammatory changes.

The latent period between infection and the onset of rheumatic fever, and the numerous immunological cross-reactions that have been described between antigens of group A streptococci and those of man (heart, brain, kidney), strongly suggest that the inflammation is mediated by the immune system (Kingston and Glynn, 1971). Which antibody, if any, is a mediator of tissue damage remains uncertain (Kaplan, 1976; DiSciaccio and Taranta, 1980).

Enterocolitic reactive arthritis

(a) *Shigella* spp.

The natural history and course of this type is best illustrated by two well documented epidemiological studies. In the Karelian epidemic (Paronen, 1948), 344 out of 150 000 individuals afflicted by *S. flexneri* dysentery developed Reiter's disease, between 1 day and 3 months after the onset of dysentery. The classical triad of articular, ocular and genito-urinary manifestations were present in 70%. Polyarthritis was present in 97% of cases, with the knee (50%), ankle, wrist and toe joints being the most commonly affected. Two-thirds of the cases with arthritis became asymptomatic within 5 months, without cartilage or bone destruction. Eye inflammation (conjunctivitis, iritis and keratitis) occurred in 89% of cases, and the urinary tract was involved in 79% (urethritis being the commonest feature). Sulphonamides, when given after the onset of arthritis, had no effect on the course of the disease (Paronen, 1948).

One hundred of the original cases were reviewed 20 years later (Sairanen, Paronen and Mahonen, 1969): 20% were asymptomatic, 30% had mild intermittent arthralgias, 18% had chronic peripheral joint disease and 32% had ankylosing spondylitis or sacro-iliitis. Of those with mild symptoms, 70% had the HLA-B27 antigen, compared to 94% of those with chronic arthritis, sacro-iliitis and ankylosing spondylitis (Sairanen and Tiilikainen, 1975).

In the U.S. warship epidemic (Noer, 1966), nine crewmen developed Reiter's disease 11–16 days after an epidemic of *Shigella* dysentery which afflic-

ted 602 individuals. The pattern of joint involvement was similar to the Karelian epidemic. Antibiotics had no effect on the course of the disease. Five of the cases were traced, of which four had recurrent arthritis and were HLA-B27 positive (Calin and Friers, 1976).

(b) *Salmonella*. Numerous reports of an aseptic polyarthritis following *S. typhimurium* (and occasionally *S. enteritidis*) infection have been reported, with a sex ratio approximating to one (Berglof, 1963; Vartiainen and Hurri, 1964). The natural history and clinical picture of the joint involvement is similar to that following infection with *Shigella*. Bacterial cultures of synovial fluid and blood are negative. Iridocyclitis, erythema nodosum and myocarditis may also occur. HLA-B27 was present in 83% of the studies in which typing was performed (Aho *et al.*, 1975).

(c) *Yersinia enterocolitica*. The aseptic polyarthritis following infection with *Y. enterocolitica* (serotype 3 and 9) has a similar natural history and clinical course to the other enterocolitic arthritides (Scott and Mair, 1979). Two per cent. of cases of *Yersinia* enteritis in Scandinavia develop reactive arthritis (Aho *et al.*, 1973). Cases of Reiter's disease, acute glomerulonephritis, carditis and erythema nodosum have also been recorded (Aho *et al.*, 1979). The frequency of HLA-B27 in *Yersinia* arthritis is 58–88% (Aho *et al.*, 1975; Laitinen, Leirisalo and Skylv, 1977). The presence of HLA-B27 is estimated as carrying a 50 times greater risk of developing reactive arthritis following *Yersinia* infection (Aho *et al.*, 1976). Individuals who are HLA-B27 negative have mild arthritis by comparison, with a shorter duration, fewer joints affected, and a lower incidence of sacro-iliitis, carditis and iritis than their HLA-B27 positive counterparts (Aho *et al.*, 1979). The sex ratio approximates to one. Some cases have later developed rheumatoid disease (Larsen, 1980).

(d) *Campylobacter*. *C. fetus* infection in one HLA-B27 negative patient was associated with a flare-up of his Reiter's disease (Urman, Zurier and Rothfield, 1977). Eight cases of reactive arthritis following *C. jejuni* enteritis have been reported, of which 4 out of 7 were HLA-B27 positive (Berden, Muytjens and Van De Putte, 1979). The natural history and clinical course were similar to that in reactive arthritis following *Yersinia* infection (Kosunen *et al.*, 1980).

Sexually acquired reactive arthritis (SARA)

Arthritis is a widely seen complication of genito-urinary infection, having been first described in 1818 (Brodie, 1818).

(a) *Non-gonococcal SARA*. The clinical features in a prospective study of 57 cases of arthritis following non-gonococcal genital infections are shown in Table 2 (Keat *et al.*, 1979). The commonest clinical

presentations were knee effusion or painful swelling of an ankle or metatarsophalangeal joint. Thirty-six of the 54 patients tissue typed were HLA-B27 positive (67%). Patients lacking this antigen had

TABLE 2. Clinical features of SARA (data from Keat *et al.*, 1979 with the permission of the Editor of *Annals of the Rheumatic Diseases*)

Male : female ratio	10 : 1
Incubation period	28 days
Onset	Acute oligo/monarticular
Peripheral joint disease	Asymmetrical oligoarthritis
Sacro-iliitis	9%
Spondylitis	2%
Enthesopathy	33%
Tenosynovitis	21%
Mucocutaneous lesions	19%
Conjunctivitis	21%
Iritis	5%
Classical Reiter's syndrome	23%

fewer joints involved, a shorter duration of the acute joint episode, and a reduced chance with extra-articular lesions or progress to chronic disease. The role of *Chlamydia* in SARA is uncertain. *C. trachomatis* infection is found in 40% of patients with SARA, the same incidence of chlamydial isolates as in uncomplicated non-gonococcal urethritis. *C. trachomatis* may not be an exclusive trigger factor for SARA. Perhaps several sexually acquired organisms, possibly sharing a common antigenic determinant are involved (Keat *et al.*, 1978). HLA-B27 does not influence susceptibility to genital infection by *C. trachomatis* but antibody titres to chlamydiae are, however, higher in the reactive arthritis patients. Individuals with the HLA-B27 antigen are 10 times more likely to develop SARA than are those without (Olhagen, 1980).

Three other microbial agents have been implicated in this form of SARA, namely mycoplasma T strain (Jonsson, 1961), L-forms of gonococci (Holmes *et al.*, 1975), and herpes genitalis simplex type 2 (Bacon *et al.*, 1974).

(b) *Aseptic post-gonococcal arthritis*. Olhagen (1980) analysed the clinical course of 16 patients with aseptic arthritis developing after gonorrhoea and 14 patients with arthritis after non-gonococcal urogenital infection. Clinically, it was not possible to differentiate the 2 groups. A complete Reiter's syndrome was found equally often in both groups. Ninety per cent. of the post-gonococcal arthritis group were HLA-B27 positive.

Idiopathic reactive arthritis

There have been several reports of aseptic arthritis following gastrointestinal bypass surgery for gross obesity (Shagrin, Frame and Duncan, 1971; Zapanta *et al.*, 1978). Cryoprotein complexes containing

antibody against *Escherichia coli* and *Bacillus fragilis* have been demonstrated (Wands *et al.*, 1976), but an association with the HLA-B27 antigen has not been confirmed (Zapanta *et al.*, 1978).

Several similarities emerge. Each category of reactive arthritis has a primary (acute infectious) stage, which precedes the symptoms and signs of arthritis by 1–2 weeks. In a small percentage of cases, there is then a secondary (complication) phase which usually starts as an acute polyarthritis, with inflammation of extra-articular tissues in some cases. HLA-B27 positive individuals are more at risk from this complication (except in acuterheumatic fever and idiopathic reactive arthritis), and have more severe and prolonged symptoms. In the majority of cases, the disease is self-limiting, the joint and other manifestations clearing up completely within a few months. Recurrences are common, and some develop chronic polyarthritis with frequent involvement of the sacroiliac joints, again more common in HLA-B27 positive individuals. Treatment is by symptomatic measures. Antibiotics do not influence the course of the disease.

Pathogenesis

The pathogenetic mechanisms underlying this group of reactive arthritides are unknown, and there are no animal models. The greater tendency of individuals with certain blood groups and HLA antigens to develop this complication indicates the importance of host factors. The role of the major histocompatibility system in rheumatology has recently been reviewed (Holborow, 1979), and two theories to explain this individual susceptibility were put forward.

(a) *The 'two-gene' theory* is based on the concept of an immune responsive (IR) gene, in linkage disequilibrium with the HLA system (McDevitt, 1980). The HLA-D locus on the sixth human chromosome is functionally analogous to the I region in the mouse (Albert, 1977). However, so far no HLA-DR or DRw associations have been found with reactive arthritis or ankylosing spondylitis (AS) that are not equally present in HLA-B27 positive healthy subjects and are thus attributable to linkage disequilibrium such as that seen with other alleles in the HLA system (Sachs *et al.*, 1975).

(b) *The 'one-gene' theory* is based on the concept of cross-reactivity between foreign antigen and self (Fig. 1). Rheumatic fever is the only disease for which a possible bacterial mimicking model has actually been identified, although the cross-reacting antigen is not a HLA antigen, but the glycoprotein on the surfaces of red blood cells and the invading micro-organism (Ebringer, 1978). This theory does not explain why HLA-B27 negative individuals can develop certain forms of reactive arthritis.

FIG. 1 Sequence of events in the 'one-gene' theory, based on Ebringer, 1978 (with the permission of the Editor of *New Scientist*).

More recent work in the mouse has clarified the precise role of the IR genes. T lymphocytes can only 'see' extrinsic antigen in the context of self major histocompatibility (MHC) antigens (MHC restriction). Each T cell subset uses a particular type of self MHC antigen in the context of which it sees

TABLE 3. T lymphocyte subsets and MHC restriction

T cell subset	H-2 restricting element (mouse)	Analogous HLA system (man)
T _H —help B cells	IA/E/C	D
help T _C	IA/E/C	D
help T _{DTH}	IA	D
T _{DTH}	IA/IB	D
T _C	K/D	A/B/C
T _S —to T _H	IJ or K/D	D or A/B/C
to T _{DTH}	IJ	D

T_H=helper cells; T_C=cytotoxic cells; T_{DTH}=cells involved in delayed-type hypersensitivity; T_S=suppressor cells.

and responds to extrinsic antigen (Table 3) (Wagner *et al.*, 1980). Analogous information may soon be available for man. The disease associations with certain HLA-ABC antigens seen in man would suggest that T_C cells are involved in their pathogenesis but how T_C cells carry out their effector function is not yet known. Recent work with human lymphocyte cultures has shown that filtrates of *Klebsiella* K43 contain a factor or factors capable of specifically modifying the sensitivity to anti-*Klebsiella* K43 serum of individuals who are B27 positive (B27⁺) but do not have AS (AS⁻). Modified B27⁺ AS⁻ lymphocytes become serologically similar to

the cells of B27 positive patients with AS. The data are compatible with a specific transformation by a *Klebsiella* K43—derived soluble of a B27—associated lymphoid cell component (Geczy, Alexander and Bashir, 1980). Independent corroboration of this study is eagerly awaited.

This modification by environmental agents of specific cell surface components may be the pathogenetic mechanism underlying the HLA-linked reactive arthritides and seronegative arthropathies, and explain their closer association with HLA-B27 than any of the HLA-DR or DRw antigens.

Treatment

The treatment of acute rheumatic fever still revolves around aspirin, steroids and bed rest (DiSciascio and Taranta, 1980). The majority of the other forms are self-limiting, and require symptomatic treatment only, and treatment for the underlying cause.

Group B

Erythema nodosum

The development of painful erythematous nodules on the legs (or arms), which fade after 3–5 weeks to leave a flat bruise-like lesion, is a well recognized

TABLE 4. Causes of erythema nodosum

Infections—Bacterial:	Group A streptococci <i>Mycobacterium tuberculosis</i> <i>Leptospira icterohaemorrhagiae</i> <i>Brucella abortus</i> <i>Neisseria gonorrhoeae</i> <i>Treponema pallidum</i> <i>M. leprae</i> <i>Salmonella typhimurium</i> <i>Yersinia enterocolitica</i> <i>Bordetella pertussis</i> <i>Mycoplasma pneumoniae</i>
Viral:	Measles
Fungal:	Coccidioidomycosis
Protozoal:	Toxoplasmosis
Drugs—Oral contraceptive pill	
Penicillins	
Sulphonamides	
Salicylates	
Iodides	
Crohn's disease, ulcerative colitis	
Sarcoidosis	
Behçet's disease	
Pregnancy	
Idiopathic	

complication of a number of disorders (Table 4). In addition to the cutaneous manifestations, there may be systemic features (malaise, chills, cough, cervical lymphadenopathy, transient albuminuria) and, in 50–75% of cases, arthralgia (Beeson and McDermot, 1975). The arthralgia involves the knees, and

occasionally the ankles, wrists, fingers, shoulders, elbows and hips. Additional features, such as swelling and tenderness of the joints (67%), morning stiffness (50%) and effusions (33%) may occur. The duration of the arthralgia varies widely, from less than six weeks (44%) to over two years (18%), with a means of six months. No crippling form of arthritis develops, even amongst those patients with prolonged signs (Truelove, 1960).

The histopathological lesions seen in the skin nodules are non-specific and reversible. There are inflammatory changes in the interlobular septa of the upper subcutaneous tissue and the dermis. Vasculitis, especially an endothelial reaction in the veins, is associated in the early stages with infiltration with neutrophils, lymphocytes, and histiocytes. Later, epithelioid cells and foreign body giant cells predominate (Beeson and McDermott, 1975). These lesions resolve without scarring, although they may recur in less than 10% of cases.

The pathogenesis of erythema nodosum is uncertain. The fact that the skin lesions occur at the same time as certain skin tests become positive (coccidioidomycosis, tuberculin), links the cutaneous nodules with the delayed type of hypersensitivity reaction. Yet the more severe variety of erythema nodosum seen in lepromatous leprosy has every appearance of a pure immune complex reaction: antibody and complement can readily be demonstrated in these lesions (Allen and Reeves, 1977).

Furthermore, there are distinct age and sex differences in the incidence of erythema nodosum, which suggest that hormonal influences may play a part. This reaction is far commoner in women, with a dramatic increase in incidence after puberty and an equally marked fall in those over the age of 40 years. It is particularly common in pregnant women, and in those on the contraceptive pill (Bombardieri *et al.*, 1977). As yet, no HLA associations have been reported in cases of erythema nodosum.

Group C

Virus-associated reactive arthritis

At present there is evidence for this form of arthritis in three conditions (Table 1). The forms associated with hepatitis B and adenovirus infections have many similarities with experimental serum sickness-induced arthritis. There is a negligible risk of chronicity or tissue necrosis, and HLA associations have been reported.

(a) *Hepatitis B*. This is a symmetrical arthritis affecting, in decreasing order of frequency, the small joints of the hands, knees, ankles, shoulders, wrists, and small joints of the feet. There may be additional swelling or redness of the affected joints, and various systemic features such as malaise, fever, anorexia, tender hepatomegaly. The joint symptoms

remit spontaneously, usually in less than four weeks, with the development of icterus (Alarcon and Townes, 1973). Synovial fluid may be inflammatory or non-inflammatory in character (Sauter and Utsinger, 1978). Eighty per cent have serum HB_sAg at the time of the arthritis. Low serum C3, C4 and CH50 values are found, and these return to normal during convalescence. Both serum and synovial fluids contain immune complexes, manifested by cryoprecipitates, containing complement, anti-HB_sAg immuno-globulin and HB_sAg. The immune complexes found in the serum of hepatitis B patients without arthritis lack the complement proteins (Wands *et al.*, 1975). Fifteen per cent have a positive test for rheumatoid factor, and 10% have positive antinuclear antibodies (Duffy *et al.*, 1976).

(b) *Adenovirus*. Four cases of a symmetrical arthritis affecting the knees, wrists, ankles, small joints of the hand, arising several days after type 7 adenovirus upper respiratory tract infection have been reported (Panush, 1974; Utsinger, 1977). The synovial fluid was inflammatory in character, but synovial fluid viral cultures were negative. Symptoms resolved spontaneously within five weeks. In three patients, serum immune complexes (complement, immunoglobulin, and intact adenovirus virion) were found. These were not present in cases of adenovirus 7 infection without arthritis. Low serum C3 and C4 levels were found during the arthritis phase, and these returned to normal after remission (Utsinger, 1977).

(c) *Rubella vaccination*. Between three and six weeks after rubella vaccination, 1–20% of children develop arthralgia affecting the knee, wrist, small joints of the hand, which remits after 2 weeks (Austin *et al.*, 1972). One per cent. have recurrent episodes of arthritis (Spruance *et al.*, 1972). Vaccination of post-pubertal women has a higher morbidity (40%), with joint symptoms arising 2–3 weeks after inoculation, and lasting 1–9 days. The small joints of the hands, and knees are most commonly affected (Weibel *et al.*, 1969). In some cases, the arthritis recurs (Lerman *et al.*, 1971). The rise in articular symptoms with age, similar to that found in cases of erythema nodosum, suggests a hormonal influence.

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